JOC Article

Intramolecular Cyclization of Ene-Imine Using Dibutylzirconocene

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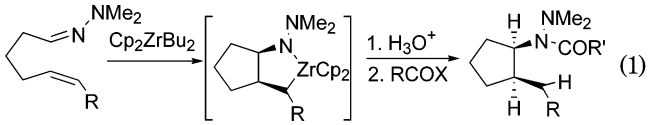
The reaction of ene-imine with Cp_2ZrBu_2 was carried out. When a crude imine, which was prepared from ene-aldehyde and primary amine in the presence of $MgSO_4$, was treated with Cp_2ZrBu_2 at room temperature overnight, cyclopentane derivative having *trans*-substituents was obtained in high yield along with a small amount of cyclopentane derivative having *cis*-substituents. Presumably, *cis*-zirconacycle is a thermodynamic product. Reactions using various ene-imines were carried out. In the case of ene-imine prepared from ene-aldehyde and $^tBuNH_2$, only cyclopentane having *cis*-substituents was produced. In this reaction, chiral amine was used, and diastereoselective cyclization of ene-imine was carried out. As a result, cyclopentane derivative having *cis*-substituents was obtained in an optically active form after hydrogenolysis of the cyclized compound.

Introduction

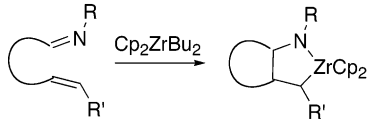
Since Negishi and Takahashi reported the generation of Cp_2ZrBu_2 from Cp_2ZrCl_2 and BuLi,[1] many reactions using this reagent have been developed.[2] The reaction of an alkyne and an alkene with Cp_2ZrBu_2 produces zirconacyclopropene or zirconacyclopropane, which can further react with various multiple bonds to form zirconacyclopentenes or zirconacyclopentanes. Intramolecular coupling reaction of diyne,[3] diene,[4] and enyne[5] using Cp_2ZrBu_2 is very effective for the formation of cyclic compounds. The coupling reaction of multiple bonds containing nitrogen is very interesting because azazirconacycle is formed as an intermediate, and various heterocycles and nitrogen-containing cyclized compounds have been synthesized. As multiple bonds, nitrile,[6] isocyanate,[7] and hydrazone[8] can be reacted with Cp_2ZrBu_2, forming various cyclic compounds. Livinghouse reported the coupling reaction of ene- or yne-hydrazone and obtained cyclopentane derivatives having *cis*-substituents (eq 1).[8]



(1)

However, little is known about the reaction of ene- or yne-imine using Cp_2ZrBu_2. Here we report the coupling reaction of ene-imime generated from ene-aldehyde and the reactivity of the formed azazirconacycle (Scheme 1).

SCHEME 1. Synthesis of Iminozirconacycle



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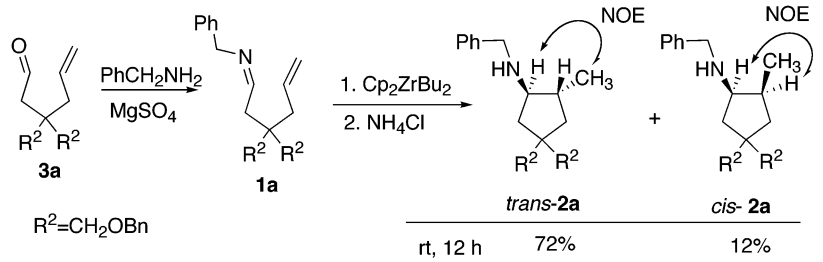
SCHEME 2. Reaction of Ene-Imine with Dibutylzirconocene



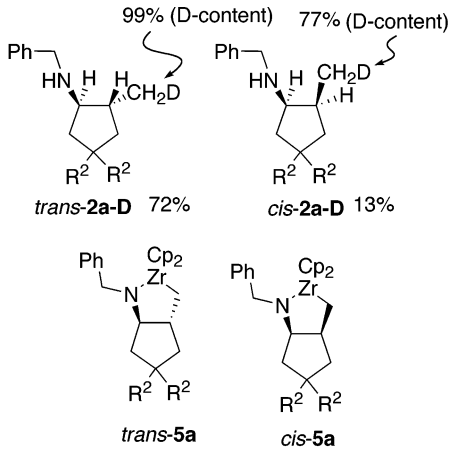


FIGURE 1.

Results and Discussion

Reaction of Ene-Imine with Cp_2ZrBu_2. A THF solution of ene-aldehyde **3a** and benzylamine was stirred at room temperature overnight in the presence of $MgSO_4$, and then undissolved material was filtered off. The filtrate was concentrated under reduced pressure to give ene-imine **1a**, whose structure was confirmed by the ^1H NMR spectrum. To a solution of Cp_2ZrCl_2 (1.3 equiv) in THF (0.1 M) was added BuLi (1.6 M solution in hexane, 2.6 equiv) at −78 °C, and the solution was stirred at the same temperature for 1 h. To this solution was added the crude imine **1a** in THF, and the solution was stirred at room temperature for 12 h. After hydrolysis of the reaction mixture, cyclopentane derivatives *trans*-**2a** and *cis*-**2a** were obtained in 72% and 12% yields, respectively (Scheme 2). The stereochemistry of each of these products was determined by NOE experiments. It is clear that cyclopentane derivative *trans*-**2a** having *trans*-substituents is the major product. The reaction mixture was treated with D_2O to give *trans*-**2a-D** and *cis*-**2a-D** in high yields (D-contents: 99% and 77%, respectively, Figure 1). When the reaction mixture was refluxed for 18 h, the yield of *trans*-**2a** slightly decreased to 63% and that of *cis*-**2a** increased to 19% yield. These results indicated that azazirconacyclopentanes *trans*-**5a** and *cis*-**5a** were formed as intermediates and that *cis*-**5a** is a thermodynamically stable azazirconacyclopentane.

The possible reaction course is shown in Scheme 3. At first, the imine part of **1a** reacts with Cp_2ZrBu_2 to give azazirconacyclopropane **4a**. Insertion of the alkene parts into carbon−zirconium bonds of **4a** gives two azazirconacyclopentanes, *trans*-**5a** and *cis*-**5a**, which were hydrolyzed to give *trans*-**2a** and *cis*-**2a**.

SCHEME 3. Possible Reaction Course for Formation of *cis*-2a and *trans*-2a

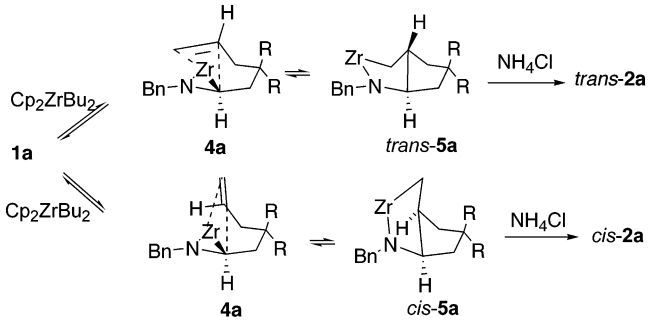
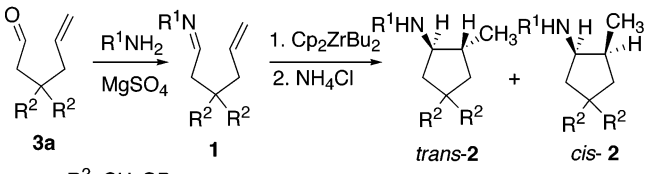


TABLE 1. Reaction of Various Ene-Imines with Cp_2ZrBu_2



run	R^1		time (h)	yield (%) total	*trans*-**2**	*cis*-**2**	ratio of *trans*-**2**:*cis*-**2**
1	Me	**1b**	12	87	77	10	7.3:1
2	Bn	**1a**	12	84	72	12	6.0:1
3	^{n}Pr	**1c**	15	71	60	11	5.7:1
4	^{i}Pr	**1d**	16	78	61	17	3.5:1
5	^{t}Bu	**1e**	3	89	0	89	0:1

Next, to examine the influence of the substituents on the nitrogen of imine in this cyclization, various amines such as methylamine, *n*-propylamine, isopropylamine, and *tert*-butylamine were used and each imine was synthesized from the corresponding amine and ene-aldehyde **3a**. The cyclization reactions were carried out at room temperature in a similar manner, and the results were shown in Table 1. The ratio of *trans*-**2** to *cis*-**2** is slightly decreased in the case of imines having the larger substituenes (Table 1, runs 1−4). Even in the case of isopropylamine, *trans*-azazirconacycle **5e** was formed predominantly (run 4). However, surprisingly, when imine having a *tert*-butyl group on the nitrogen was reacted with Cp_2ZrBu_2, the reaction rate was accelerated, and after 3 h only *cis*-**2e** was produced in 89% yield (run 5). The stereochemistries of the substituents were determined by NOE experiments. Presumably, *cis*-**2e** should be formed predominantly by steric hindrance between the alkene parts and the methyl group on the *tert*-butyl group of iminozirconacyclopropane **4e** as shown in Figure 2.

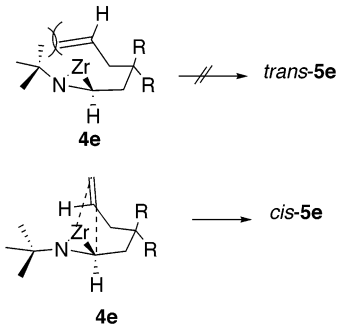
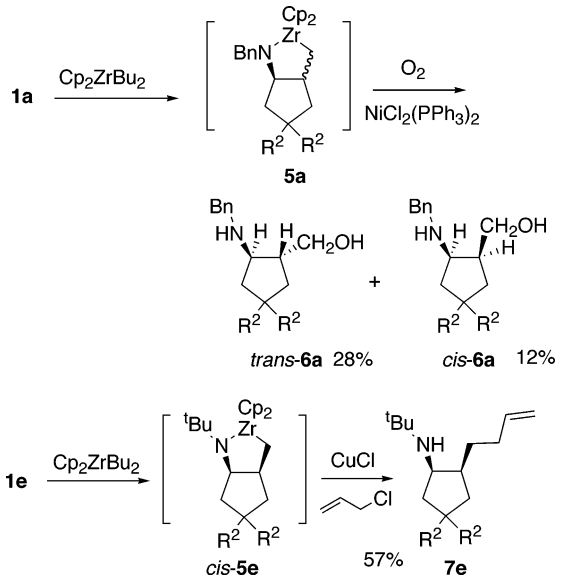


FIGURE 2.

SCHEME 4. Reaction of Zirconacycle with Various Reagents



It has been reported that zirconium-mediated cyclization of ene-hydrazone using Cp_2ZrBu_2 gave a cyclized compound having *cis*-substituents,[8] which means that *cis*-azazirconacycle was formed as an intermediate (eq 1). In this case, the steric effect between the alkene part and the hydazone part of ene-hydrazone should form *cis*-azazirconacyclopentene.

Reactivities of Azazirconacycles. The remarkable feature of zirconium-mediated cyclization is that various reagents could be reacted with intermediary zirconacycle to give cyclic compounds having functionalized substituents by a one-pot reaction (Scheme 4). When the atmosphere of the vessel used for formation of azazirconacyclopentane **5a**, prepared from **1a** and Cp_2ZrBu_2, was changed from argon to oxygen and the solution was stirred at room temperature overnight, only small amounts of alcohols *trans*-**6a** and *cis*-**6a** were obtained (2% and 7% yields, respectively). Thus, the transmetalation of azazirconacyclopentane into a nickel complex was carried out.[9] To a THF solution of azazirconacyclopentanes **5a** was added $NiCl_2(PPh_3)_2$ (1.2 equiv), and the solution was stirred at room temperature for 12 h under an oxygen atmosphere. After the usual workup, the desired *trans*-**6a** and *cis*-**6a** were obtained in 28% and 12% yields, respectively.

SCHEME 5. Diastereoselective Zironium-Catalyzed Cyclization

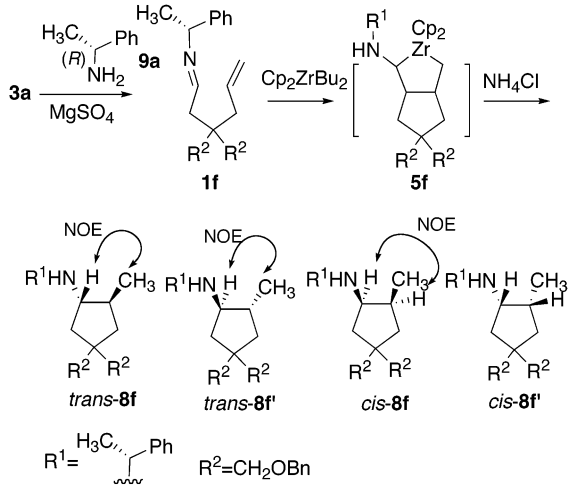


TABLE 2. Zirconium-Mediated Diastereoselective Cyclization

run		*trans*-**8f**	*trans*-**8f′**	*cis*-**8f**	*cis*-**8f′**
1	rt, 13 h	39	22	17	
2	rt, 47	32	22	20	
3	reflux, 18 h	10	7	53	17

Next, carbon−carbon bond formation using azazirconacyclopentane was investigated. When CuCl and allyl chloride[10] were added to a THF solution of azazirconacyclopentane *cis*-**5e**, which was prepared from **1e** and Cp_2ZrBu_2, and the solution was stirred at room temperature for 24 h, allylated compound **7e** was obtained in 57% yield.

It was expected that if a chiral amine is used for formation of imine,[11] diastereoselective cyclization will occur in the reaction of ene-imine with Cp_2ZrBu_2 (Scheme 5). When a THF solution of ene-imine **1f**, which was prepared from **3a** and (*R*)-phenethylamine **9a**, was stirred in the presence of Cp_2ZrBu_2 at room temperature for 18 h, cyclized compounds *trans*-**8f**, *trans*-**8f′**, and *cis*-**8f** were obtained in 39%, 22%, and 17% yields, respectively, after hydrolysis. The stereochemistry of each of these products was determined by NOE, and the ratio of *trans*-**8f** to *cis*-**8f** was determined to be 3:1. A longer reaction time did not affect the yield of each product (run 2). When the reaction mixture was refluxed for 18 h, the ratio of *trans*-**8** to *cis*-**8** changed to 1:4 and *cis*-**8f** was obtained as the major product in 53% yield along with *cis*-**8f′** in 17% yield (Table 2, run 1). The results are interesting because when the reaction of **1a** with Cp_2ZrBu_2 was carried out in THF upon heating, *trans*-**2a** was obtained as the major product (Scheme 2). However, the major product was a *cis*-form when the THF solution of **5f** was refluxed for 18 h.

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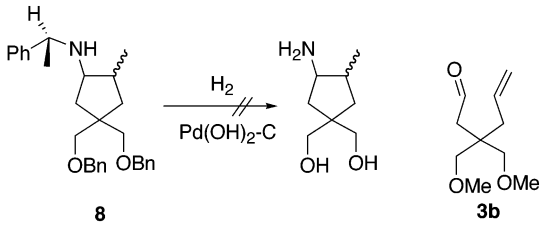
(11) Intermolecular coupling raction of chiral imine and aldehyde using Cp_2ZrBu_2: Ito, H.; Tagutchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 4469.

SCHEME 6. Attempt of Hydogenolysis of Amine 8



Presumably, formation of *cis*-zirconacycle would be accelerated by the large substituent like the *tert*-butyl group on the nitrogen.

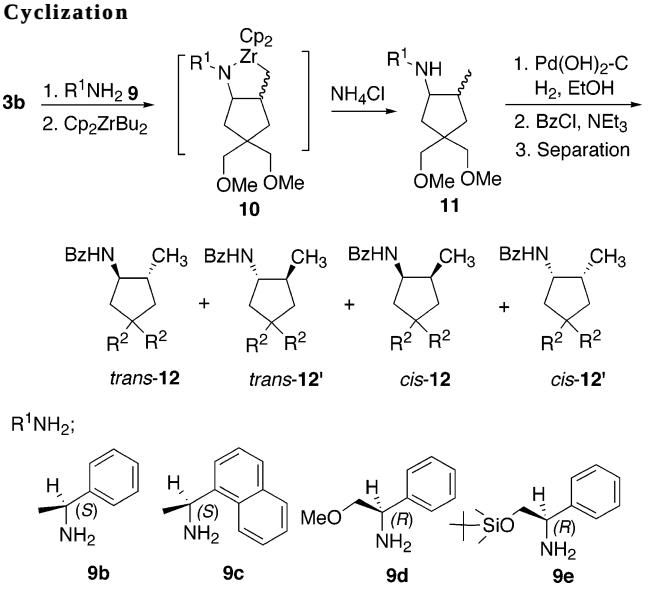
To examine the effect of various chiral imines with Cp_2ZrBu_2, their ratios were determined by HPLC. Hydrogenolysis of *N*-benzyl and *O*-benzyl groups was carried out using $Pd(OH)_2$ on charcoal.[12] Although the starting material **8** disappeared on TLC, the desired amine-alcohol could not be isolated (Scheme 6). Various attempts were made, but the results were fruitless.

Thus, the starting material was changed from **3a** to **3b**, and the various chiral amines **9** were used for this reaction. The reactions were carried out at room temperature or upon heating in THF for 18 h. The yields of the diastereomers were determined as follows. A mixture of diastereomers **11** was hydrogenated using $Pd(OH)_2$ on charcoal followed by benzoylation to give *trans*-**12**, *trans*-**12′**, *cis*-**12**, and *cis*-**12′**. The *trans*- and *cis*-isomers were separated by column chromatography on silica gel. The ee's of *trans*-**12** and *cis*-**12** were determined by HPLC (*trans*-**12**, DAICEL CHIRAPAK AD, hexane/^{i}PrOH = 95/5; *cis*-**12**. DAICEL CHIRAPAK AS, hexane/^{i}PrOH = 9/1), and the yield of each diastereomer could be calculated from the results of HPLC. The results are shown in Table 2. When the reaction was carried out at room temperature, the larger substituents on the nitrogen decreased the yields of the *trans*-cyclopentane derivative, but the major product was *trans*-**12** in each case (Table 3, runs 1, 3, 5, and 7). The reaction was carried out upon heating in THF to give *cis*-**12**, but a relatively amount of *cis*-**12′** was formed in each case (runs 2, 4 and 8). In the case of amine **9d**,[13] the yields of *trans*-**12**, *trans*-**12′**, *cis*-**12**, and *cis*-**12′** were almost same when the reaction was carried out at room temperature and upon heating (runs 5 and 6).

Presumably, the methoxy group of the substituent coordinates to the zirconium metal as shown in Figure 3, and each zirconacyclopentane could not isomerize even upon heating. The best results of the ratio of *cis*- to *trans*-substituents and the yield of *cis*-**12** were obtained when amine **9e**[14] was used and the reaction was carried out upon heating (run 8). Thus, the reaction of **9e** with Cp_2ZrBu_2 was further examined. A THF solution of zirconacycle **10e** was refluxed for 65 h, but the yield was not improved (run 9). When the reaction was carried out at 40 °C for 18 h, *cis*-**12** was obtained in 63% yield (run 10).

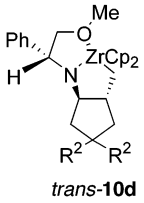
The absolute configuration of *cis*-**13** was determined using Kusumi's method (Scheme 7).[15] Amine *cis*-**11** was

TABLE 3. Diastereoselective Zirconium-Mediated Cyclization



run		temp (°C)	yield (%)[a] of total	*trans*-**12**	*trans*-**12′**	*cis*-**12**	*cis*-**12′**	ratio of *trans*:*cis*
1	**9b**	rt	100	44	20	28	8	1.8:1
2	**9b**	reflux	94	7	6	56	25	1:6.1
3	**9c**	rt	100	41	17	35	7	1.4:1
4	**9c**	reflux	95	11	7	59	18	1:4.3
5	**9d**	rt	99	39	14	30	8	1.4:1
6	**9d**	reflux	87	35	16	28	8	1.4:1
7	**9e**	rt	98	40	15	38	5	1.3:1
8	**9e**	reflux	84	8	4	59	13	1:6.1
9	**9e**	reflux[b]	75	7	3	52	13	1:6.5
10	**9e**		98	16	10	63	9	1:2.8

[a] All reactions were carried out using 1.3 equiv of Cp_2ZrCl_2 in THF for 18 h. [b] Reaction time: 65 h.



trans-**10d**

FIGURE 3.

hydrogenated, and the resultant *cis*-**13** was treated with (*S*)- and (*R*)-MTPA chlorides in the presence of pyridine to give *cis*-(*S*)-**14** and *cis*-(*R*)-**14**, respectively. From the differences between δ values of ^{1}H NMR spectra, the absolute configuration of the major isomer *cis*-**11** was determined to be (1*R*,2*S*). In a similar manner, the minor isomer of *trans*-**11** was also determined to be (1*S*,2*S*).

The possible reaction course is shown in Scheme 8. When the imine part of ene-imine **15e** reacts with Cp_2Zr to form azazirconacyclopropanes, there are two pathways, path a and path b. Then insertion of the alkene part into the carbon−zirconium bond of azazirconacyclopropane **16e** produces azazirconacyclopentanes *trans*-**10e** and *cis*-**10e**. In a similar process, *trans*-**10e′** and *cis*-**10e′** should be formed. In these pathways, diastereoselection would occur at the first stage, when the imine part reacts with Cp_2Zr to give azazirconacyclopropane. Presumably, the most stable conformation of **15e** should be **15e-I**, not **15e-**

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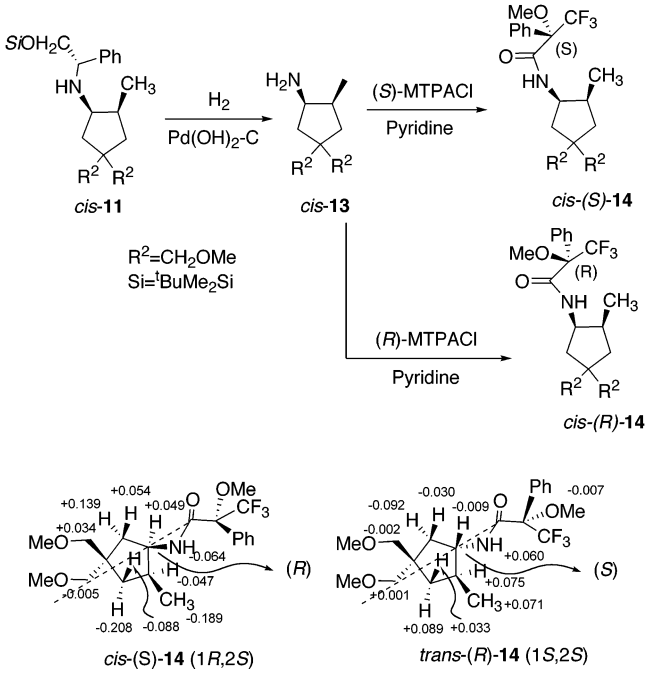
SCHEME 7. Determination of Absolute Configuration



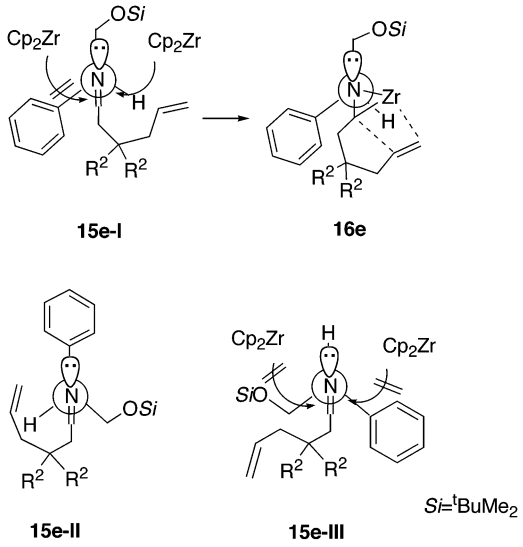
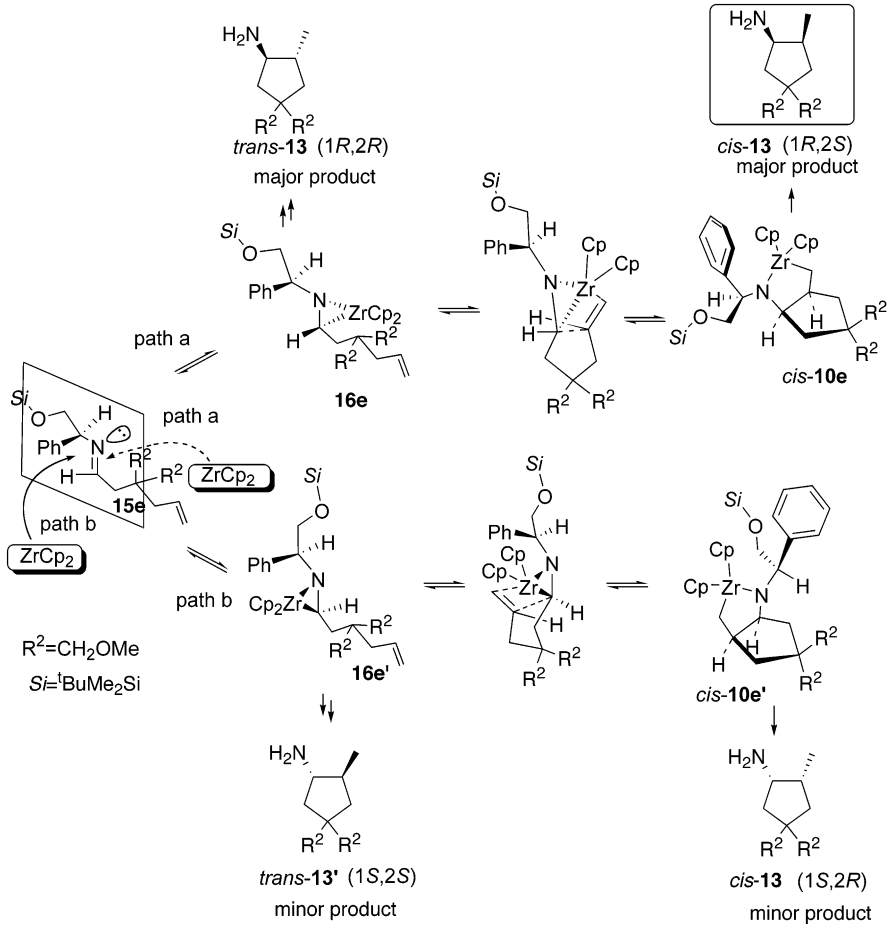


FIGURE 4.

II or **15e-III**, because of the electronic repulsion between the phenyl group and the lone pair of nitrogen in **15e-II** or the steric interaction between Cp_2Zr and the phenyl group or the silyloxyethyl group in **15e-III**. (Figure 4). Thus, Cp_2Zr would attack from the backside of this plane (path a in Scheme 8, the proton side of **15e-I** in Figure 4). In the early stage of this reaction at room temperature, *trans*-zirconacycle *trans*-**10e** is formed from **16e** as a kinetic product. However, when the THF solution of the reaction mixture was refluxed for 18 h, *cis*-**11e** was formed as a thermodynamic product. The reason for

SCHEME 8. Possible Reaction Course



formation of *cis*-**11e** as a major product upon heating is presumably the steric effect of the substituent on the nitrogen. When the reaction mixture was further refluxed for a long time, the yield of *cis*-**11e** decreased but that of cis-**11e′** was not changed (Table 3, run 9). Presumably, zirconacycles *trans*-**10e** and *cis*-**10e** were not stable under these reaction conditions. It is not clear whether *cis*-**11e** was gradually changed to *cis*-**11e′** or *cis*-**11** was decomposed under these reaction conditions.

Conclusion

Little is known about zirconium-mediated cyclization of ene-imine. The reaction of ene-imine **1a** with Cp_2ZrBu_2 at room temperature gave cyclopentane derivatives *trans*-**2a** and *cis*-**2a**, the major product being a compound having *trans*-substituents. It was interesting that the cyclization is affected by the bulkiness of the substituents on nitrogen. Cyclization of ene-imine **1e** having a *tert*-butyl group on nitrogen gave only *cis*-**2e**. The intermediary azazirconacyclopentane is very useful in synthetic organic chemistry. Using transmetalation from azazirconacycle to other metals, various functionalized cyclopentylamine derivatives should be formed. Since this reaction was affected by the substituents on nitrogen, diastereoselective cyclization occurred and *cis*-fused azazirconacycle was formed as a major product upon heating. Thus, optically active cyclopentylamine derivative *cis*-**13** was obtained in good yield. Zirconium-catalyzed asymmetric cyclization has already been developed, and this reaction had been carried out using a catalytic amount of EBTHIZr(BINOL) in the presence of an excess amount of Grignard reagent.[16] However, Grignard reagent cannot be used for the reaction of ene-imine cyclization. Thus, zirconium-mediated diastereoselective cyclization should be a useful tool for the synthesis of a chiral cyclized product.

Experimental Section

General Procedure for Synthesis of Imines (1a−e) from Aldehydes (3a) and Amines. A solution of ene-aldehyde **3a** (1 equiv) and amine (1 equiv) in benzene (0.1 M) was stirred in the presence of $MgSO_4$ (10 equiv) at room temperature overnight. The solution was filtered, and the filtrate was concentrated. The residue used without further purification.

Benzyl-(3,3-bisbenzyloxymethyl-hex-5-enylidene)amine (1a). IR (neat) ν 3063, 3028, 2857, 1662, 1495, 1453, 1364, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.21 (d, J = 7.6 Hz, 2 H), 2.39 (d, J = 5.6 Hz, 2 H), 3.39 (d, J = 2.8 Hz, 4 H), 4.45 (s, 4 H), 4.49 (s, 2 H), 5.00−5.02 (m, 1 H), 5.04 (s, 1 H), 5.74−5.84 (m, 1 H), 7.83 (dt, J = 1.6, 5.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.7, 39.9, 42.4, 65.3, 73.0, 73.2, 118.1, 126.7, 127.3 (x 2), 127.9 (x 4), 128.2 (x 4), 128.3 (x 2), 128.3 (x 2), 133.8 (× 2), 138.5, 164.3; LRMS (EI) m/z 428 (M^+ + H), 386, 350, 336, 306, 133, 91; HRMS (EI) calcd for $C_{29}H_{33}NO_2$ (M^+) 427.2511, found 427.2520.

General Procedure for Zirconium-Mediated Cyclization of Ene-Imine. To a solution of Cp_2ZrCl_2 (1.3 equiv) in THF (0.1 M) was added BuLi (1.6 M solution in hexane, 2.6 equiv) at −78 °C, and the solution was stirred at the same temperature for 1 h. To this solution was added at −78 °C ene-imine **1** (1 equiv), which was prepared from **3a** and $PhCH_2NH_2$ (1 equiv) in benzene in the presence of $MgSO_4$ at room temperature, and the solution was stirred at room temperature for the appropriate hours. Saturated NH_4Cl solution was added, and the solution was stirred at room temperature for 2 h. The aqueous layer was made basic by K_2CO_3, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel to give the cyclized product.

Benzyl-(4,4-bisbenzyloxymethyl-2-methylcyclopentyl)-amine (*trans*-2a, *cis*-2a). *trans*-**2a**: IR (neat) ν 2919, 2856, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 6.4 Hz, 3 H), 1.10 (dd, J = 10.6, 12.4 Hz, 1 H), 1.27 (dd, J = 9.6, 13.2 Hz, 1 H), 1.40 (bs, 1 H), 1.71−1.78 (m, 1 H), 1.81 (dd, J = 7.2, 13.2 Hz, 1 H), 2.04 (dd, J = 7.2, 13.2 Hz, 1 H), 2.58 (dd, J = 9.2, 9.6 Hz, 1 H), 3.33 (s, 2 H), 3.38 (dd, J = 8.8, 12.2 Hz, 2 H), 3.67 (d, J = 13.2 Hz, 1 H), 3.83 (d, J = 12.8 Hz, 1 H), 4.51 (s, 4 H), 7.22−7.34 (m, 15 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 39.7, 39.8, 44.5, 52.7, 64.9, 73.1, 73.2, 75.2, 75.4, 126.7, 127.2 (x 2), 127.3 (x 4), 127.9 (x 2), 128.2 (x 4), 127.3 (x 2), 138.6 (x 2), 140.8; LRMS (FAB) m/z 430 (M^+ + H), 338, 91; HRMS (FAB) calcd for $C_{29}H_{36}NO_2$ (M^+ + H) 430.2746, found 430.2726. *cis*-**2a**: IR (neat) ν 2922, 2856, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 7.2 Hz, 3 H), 1.39 (dd, J = 7.6, 13.6 Hz, 1 H), 1.58 (dd, J = 6.0, 13.2 Hz, 1 H), 1.64−1.71 (m, 2 H), 2.10−2.20 (m, 1 H), 3.04 (dd, J = 6.0 Hz, 12 Hz, 1 H), 3.33 (s, 2 H), 3.45 (s, 2 H), 3.63 (d, J = 13.2 Hz, 1 H), 3.75 (d, J = 13.2 Hz, 1 H), 4.51 (d, J = 2.0 Hz, 4 H), 7.22−7.34 (m, 15 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 36.5, 37.4, 38.6, 45.7, 52.2, 61.1, 73.1, 73.2, 75.2, 75.7, 126.6, 127.2 (x 2), 127.3 (x 4), 127.4 (x 2), 128.0 (x 4), 128.2 (x 2), 138.8 (x 2), 141.0; LRMS (FAB) m/z 430 (M^+ + H), 338, 91; HRMS (FAB) calcd for $C_{29}H_{36}NO_2$ (M^+ + H) 430.2746, found 430.2765.

Note Added after ASAP Posting. There was an error in the cyclic intermediate in the Table of Contents graphic in the version posted ASAP August 17, 2004; the corrected version was posted September 1, 2004.

Supporting Information Available: Experimental procedures and spectral data for compounds **1a**−**f**, *trans*-**2b**−**d**, *cis*-**2b**−**e**, *trans*- and *cis*-**6a**, **7e**, *cis*-**8f** and **-8f′**, *trans*-**8f** and **-8f′**, *trans*- and *cis*-**12**, *trans*-(*R*)-**14**, **18**−**23**, **3a**, and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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